Ministry of Health

THE GREATER COUNCIL FOR HEALTH
SESSION 46
Meeting of October 23, 2007
JOINT SECTIONS II AND V

THE GREATER COUNCIL FOR HEALTH

In view of the report by Direzione Generale Farmaci e Dispositivi Medici [Department of Drugs and Medical Devices] on "the use of IGF-1 and IGF-1/IGF-BP3 for the treatment of amyotrophic lateral sclerosis (ALS)."

Considering that, on the instructions of his Excellency the Minister, the competent Department requested the Council to "*proceed with an in-depth and updated evaluation of the possible benefits that, based on current scientific knowledge, may be expected from the use of the two drugs in the treatment of ALS against the risks, both those directly linked with taking said products and those associated with the failure of following possible alternative therapies with the duly approved drug."*

In view of Decree-law No. 536 of October 21, 1996, converted into Law No. 648 of December 23, 1996, and in particular Article 1, paragraph 4 which provides as follows: *"In the event a valid therapeutic alternative does not exist, dispensing borne by the National Health Service is permitted, starting on January 1, 1997,of innovative drugs whose sale is authorized in other countries, but not in the domestic territory, drugs not yet authorized but which underwent clinical trials, and drugs to be used for a therapeutic indication other than the one which has been authorized, included in a special list prepared and periodically updated by the Unified Drug Committee in compliance with procedures and criteria adopted by the Committee...."*.

In view of the Ministerial Decree of May 8, 2003 “Therapeutic use of a drug submitted to clinical trial."

Taking into account that the above-mentioned Ministerial Decree states that a drug that underwent clinical trials in the Italian territory or in a foreign country may be used, outside clinical trials, for the treatment of serious pathologies or rare diseases or disease conditions that place the patient in danger for his or her life, when the following conditions are met:

"a. *The drug has already been the subject, in the same specific therapeutic indication, of third stage clinical trials, in progress or completed, or, in special cases of disease conditions that place the patient in danger for his or her life, of second stage clinical trials already completed;*

b. available data on the tests mentioned in letter a) is sufficient for formulating a favorable opinion on the effectiveness and tolerability of the requested drug."

Given that:

- Riluzole (Rilutek), authorized in the European Union and in the United States of

America for the treatment of ALS, sold and reimbursed in Italy by the National Health System, is to date the only drug that, within the context of controlled clinical trials, has been demonstrated to be effective, compared to the placebo, in extending the survival rate of patients suffering from the disease (approximately three months);

- IGF-1 (Insulin-like Growth Factor-1) and IGF-1/IGF-BP3 are drugs indicated for the "*treatment of growth failure in children with severe and primary IGF-1 deficiency or with deletion of the GH (growth hormone) gene and who developed antibodies that neutralize the growth hormone.*" The sale of said drugs has been authorized since the end of 2005 by the Food and Drug Administration (FDA) in the United States.

Acknowledging that:

- starting from the second half of 2006, rulings by Labor Judges ordering patients suffering from ALS to be supplied free of charge with IGF-1 or, alternatively, IGF-1/IGF-BP3 became more frequent, because of petitions, filed by the individuals directly involved, alleging that taking these drugs is indispensable, because no valid therapeutic alternative exist;
- IGF-1 is not approved for ALS treatment in any country worldwide;
- in two controlled clinical trials, completed to date, conducted on patients suffering from ALS, administration of IGF-1 did not involve clinically relevant results for patients;
- no European country requested the manufacturer to supply IGF-1 for the treatment of ALS and in Italy the majority of requests appears to come from a small number of prescribing physicians;
- IGF1/IGF-BP3 does not appear to have ever been the subject of clinical trials on patients suffering from ALS.

Considering that *Direzione Generale Farmaci e Dispositivi Medici* stated to AIFA, in a memo dated September 20, 2006, the need for verification by a technical and scientific committee of the possible existence of the requirement for dispensing of the drug IGF-1, borne by the National Health Service pursuant to the above-mentioned article 1, paragraph 4, Decree-law No. 536 of October 21, 1996, converted into Law No. 648 of December 23, 1996.

Having observed that:

- on November 21, 2006 the AIFA technical-scientific Committee, also on the basis of the investigative activity carried out by the Clinical Trial Subcommittee, with the contribution of outside experts, deemed non existent "*the requirements for free distribution paid by the National Health Service (within the scope of Law 648/96), of the drugs IGF-1 and IGF-1/IGF-BP3 for the treatment of patients suffering from* ALS" and it observed that *"the use of IGF1 and IGF-1/IGF-BP3 in* ALS *is not supported by regulatory tools (drug without registered label indication) or scientific grounds (from the trials completed thus far there is no evidence that IGF-1 is effective in ALS therapy, whereas to date IGF-1/IGF-BP3 has not even been studied on patients suffering from the disease)";*
- *on* March 13, 2007 the AIFA technical-scientific Committee, supplementing the opinion already expressed on November 21, 2006, reiterated that, based on knowledge and the results of available studies, providing those drugs free of charge (with costs borne by the National Health Service) for the treatment of patients suffering from ALS was not justified.

Taking into account that:

- in view of the evaluations expressed by the e AIFA technical-scientific Committee, the Ministry of Health, in order to *"avoid that patients and their family members continue to*

rely on a treatment that at this time is not recognized as suitable," took pains so that it would be acknowledged by the Courts that the requirements for dispensing the drugs in question free of charge did not exist;
- in the majority of legal proceedings, instead, provisions and decrees adopted based on petitions submitted by ALS patients were in favor of the petitioners.

After examining the records

After hearing the ad hoc work group, with Prof. Cuccurullo as spokesperson

Considering that

- evidence of the safety and effectiveness of the drugs IGF-1 and IGF1/IGF-BP3 for the treatment of ALS is not available;
- IGF-1/IGF-BP3 was never tested in that therapeutic indication;
- two controlled double blind clinical trials vs. placebo evaluated the safety and effectiveness of human recombinant IGF1 in ALS, using as a measure of the primary outcome a change in the progression of the disease after nine months of treatment;
- the two above-mentioned trials gave rise to contradictory results; in fact, while in the first one, conducted in the United States[1], IGF-1 treatment seemed to improve certain patient functional parameters; in the second trial, conducted in Europe[2], gave results that were superimposable to those obtained with a placebo;
- a recent metaanalysis[3] conducted on the data of the two above-mentioned trials, led the Authors to the conclusion that the data does not allow a definitive evaluation of the clinical effectiveness of rhIGF-l on ALS, maintaining the need to begin further studies that assume patient survival as a measurement of the outcome;
- the results of a multicenter clinical trial, sponsored by the National Institute of Neurological Disorders and Stroke, coordinated by E. Sorenson (Department of Neurology, Mayo Clinic) within the framework of which 330 patients were treated, randomized to receive either IGF-1 or a placebo for two years, to verify whether the treatment can slow down the progression of the disease, are not yet available;
- no study, therefore, has so far demonstrated that IGF-1 is able to improve the survival rate of patients suffering from ALS.

Taking therefore into account that treatment of ALS with IGF-1 and IGF1/IGF-BP3, the risk/reward profile of which has not yet been adequately evaluated within the scope of controlled clinical trials, exposes in any case the patient to a treatment of unknown effectiveness and not devoid of side effects, diverting him or her from taking a drug (Riluzole) with proven effectiveness and duly registered for said therapeutic indication.

MAINTAINS

- that, based on the results of trials available to date, treatment of patients suffering from ALS with the drugs IGF-1 and IGF-1/IGF-BP3 is not justified;
- that, for the same reasons, use of said drugs in not justified for the treatment of patients suffering from ALS who do not respond to Riluzole therapy;
- that resources currently used to treat patients suffering from ALS with these drugs can be more usefully used to ensure to said patients interventions the effectiveness of

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[1] *Lai EC, Felice KJ, Festoff BW, Gawell MJ, Gelinas DF, Kratz R, Murphy MF, Natter HM, Norris FH, Rudnicki SA. Effect of recombinant human insulin-like growth factor-l on progression ot ASL. A placebo-controlled study. The Norlh America ALS/IGF-I Study Group. Neurology 1997; 49:1621-30*

[2] *Borasio GD, Robbervcht W.Leigh PN, Emile J, Guillcff RJ. Jerusalem F, Silani V, Vos PE, Wokke JHJ, DobbinsT. "A placebo-controlled trial of insulin-lìke growth factor-l in amyotrophic lateral sclerosis. European ALS/IGF-I Study Group."Neurology 1998; 51:583-6*

[3] Mitchell JD, Wokke JHJ, Borasio GD" *Recombinant human insulin-like growth factor I (rhlGF-l) for amyotrophic lateral sclerosis/motorneuron disease"* Cochrane Database of Systematic Reviews 002; (3): CD002064

which is supported by adequate scientific evidence.

MAINTAINS

Finally that, also from a regulatory standpoint, the requirements for treating ALS with those drugs do not exist.

However

IT RESERVES

to re-examine the issue in view of the final results of the study currently under way in the United States.

Secretary General
Signed Concetta Mirisola

President, Greater Council for Health
Signed Franco Cuccurullo

TRUE COPY
[signature]